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09/662,454	09/14/2000	Masayuki Yanagi	2026-4276US1	9114

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/662,454	Applicant(s) YANAGI ET AL.	
	Examiner Gerald Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-57* is/are pending in the application.

4a) Of the above claim(s) *46,47,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,45,48,51-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I (claims 42-45, 48, 51-57) in Paper No. 5 is acknowledged. The traversal is on the ground(s) that 1) there is no art of record that the HCV nucleic acids of the invention (i.e. nucleic acids comprising the different recited SEQ ID NOS of the different groups) have distinct regulatory sequences, 2) each of the claimed nucleic acids function similarly in that the nucleic acids compositions are all used for therapeutic purposes and would have the same effect, and 3) the nucleic acid sequences represented by SEQ ID NOS: 1-6 were all examined together in the parent application. This is not found persuasive because of the following reasons.

While the nucleic acids of the invention may have similar regulatory sequences, each is still distinct from the others chemically, structurally and functionally in that the sequences represented by the different pairs of sequence identifiers (i.e. SEQ ID NOS: 3-4, 1-2 and 5-6) correspond to chemically, structurally and functionally distinct HCV polypeptides. These polypeptides have distinct structural/functional properties that are likely to affect their relative ability to infect cells in vivo and thus their ability to induce a protective immune response. Therefore, the nucleic acids encoding the different HCV polypeptides are functionally distinct from one another.

With regard to examination of each of the nucleic acid sequences together in the parent application, this argument is irrelevant to the instant application. In examining the instant invention each of the recited nucleic acid sequences has to be searched with respect to production of a protective immune response in a host animal, which is different from the search

required in the parent application. Even if the inventions in the instant application and the parent application were exactly co-extensive, additional searches of the current application and issued files databases would be required for the instant application. Given the large size of the recited sequences (i.e. greater than 9 kb or 3,000 amino acids), and given the ever-increasing size of the databases that must be searched, this additional search represents a burdensome search requirement for the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 44-57 are pending in this application. Claims 46-47 and 49-50 are withdrawn from consideration.

Information Disclosure Statement

Receipt is acknowledged of an information disclosure statement (IDS) filed 9/14/00 (Paper No. 1). The signed and initialed PTO Form 1449 has been mailed along with this action.

Claim Objections

Claims 42, 48, 51 and 53 objected to because of the following informalities: the phrase "A composition comprising a purified and isolated nucleic acid molecule...said nucleic acid molecule encodes human hepatitis C virus..." is grammatically confusing. It would be remedial to insert the word "wherein" prior to the words "said nucleic acid molecule". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42, 44-45, 48 and 51-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 9-11, 19-20 and 22 of U.S. Patent No. 6,153,421. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

The claims of the instant application are drawn towards compositions comprising a purified and isolated nucleic acid molecule suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient, wherein the nucleic acid molecule encodes human hepatitis C virus and wherein expression of the nucleic acid molecule in transfected cells results in production of virus when transfected in cells. The nucleic acid can encode a wildtype virus or a chimeric virus wherein a fragment of the viral genome is replaced with the corresponding fragment from a different strain of hepatitis C virus. The fragment can either encode the structural proteins of the hepatitis C virus or can encode any protein from the hepatitis C virus. The nucleic acid can encode the amino acid sequence of SEQ ID NO: 3. The nucleic acid can comprise SEQ ID NO: 4.

The claims of the '421 patent are drawn towards purified and isolated nucleic acid molecules, wherein the nucleic acid molecules encode human hepatitis C virus and wherein expression of the nucleic acid molecules in transfected cells results in production of virus when transfected in cells. The nucleic acids can encode a wildtype virus or a chimeric virus wherein a fragment of the viral genome is replaced with the corresponding fragment from a different strain of hepatitis C virus. The fragment can either encode the structural proteins of the hepatitis C virus or can encode any protein from the hepatitis C virus. The nucleic acid can encode the amino acid sequence of SEQ ID NO: 3. The nucleic acid can comprise SEQ ID NO: 4.

The major difference between the instant claims and the claims of the '421 patent is the limitation of "a suitable amount of a pharmaceutically acceptable diluent or excipient" in the claims of the instant application. Claim 42 of the instant application is also a genus claim, totally encompassing the specific embodiments recited in claims 1-2 of the '421 patent. Pharmaceutically acceptable diluents or excipients would include, for example, water or saline solutions that one of skill in the art would use in purification of the nucleic acids recited in the claims of the '421 patent. It would have been primae facie obvious to one of ordinary skill in the art at the time of applicants' invention to use, for example, water in the purification and isolation of the nucleic acids recited in the claims of the '421 patent. One would have been motivated to do so in order to receive the expected benefit of being able to directly mix the nucleic acids into pharmaceutical compositions without further purification. With regard to claim 42, the species claims of the '421 patent necessarily make obvious the genus claim.

While it is recognized that a restriction requirement was made in the previous application which issued as the '421 patent, and that the instant claims are directed towards the nucleic acid

composition that was restricted from the issued claims in the parent, it appears the examiner in the previous application interpreted the limitation of "a suitable amount of a pharmaceutically acceptable diluent or excipient" as specifying that the composition is necessarily a pharmaceutical composition. This interpretation is inaccurate. As indicated above, water is a pharmaceutically acceptable diluent or excipient. Thus, the claims of the instant application and the '421 patent clearly overlap significantly. If a patent issued on the instant claims were assigned to an assignee different from the assignee of the '421 patent, then the possibility of harassment by multiple assignees would improperly arise. To avoid this situation it would be remedial to amend the instant claims to clearly indicate that the composition is a pharmaceutical composition. Alternatively, it would be remedial to file a terminal disclaimer over the '421 patent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C.

122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Yoo et al (J. Virology, 1995, Vol. 69, No. 1, pages 32-38; see the entire document).

Yoo et al teach a synthetic RNA comprising the hepatitis C virus genome produced from a transcription vector. The RNA transcript was transfected into Huh7 cells and HCV was produced as evidenced by detection of HCV RNA and viral RNA replication as well as the presence of active HCV in the culture media (e.g. see the Abstract).

Claim 42 is rejected under 35 U.S.C. 102(e) as being anticipated by Houghton et al (U.S. Patent No. 5,679,342; see the entire patent).

Houghton et al teach a full length HCV RNA (R+HCVF) which was transcribed form a transcription vector (column 25, line 14-column 27, line 10). The RNA was transfected into Huh7 cells and active HCV particles were produced as detected by the presence of HCV RNA in the cells, viral RNA replication and infectious HCV particles in the culture supernatant. Houghton et al further teach that transfection of cells with HCV cDNA will also result in propagation of the virus (column 17, lines 19-30).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43, 55-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Each of the rejected claims is drawn towards methods of immunizing an animal against hepatitis C virus (HCV) by utilizing a nucleic acid composition wherein the nucleic acid encodes a hepatitis C virus and wherein expression of the nucleic acid in transfected cells results in production of virus. The claimed invention is thus exceedingly complex, involving the administration of a nucleic acid in order to elicit a protective or therapeutic immune response to the polypeptide(s) encoded by the nucleic acid.

Breadth of the claims: The breadth of the claims only exacerbates the complexity of the invention. The claimed methods are to be practiced on any animal, including humans, regardless if whether the animal is susceptible to HCV infection or not. Additionally, the nucleic acid composition is to be effective in producing a therapeutic or protective response in animals already infected with HCV, or in animals which have yet to be exposed to HCV. Moreover, the limitation that the nucleic acid of the composition be able to produce virus upon transfection in a

cell means that there is the possibility of productive infection of the virus resulting in, or worsening, HCV infection of the treated animal.

Guidance of the specification: The specification provides little actual guidance with regard to practicing the claimed invention other than providing lists of pharmaceutical carriers and routes of administration, etc. Little guidance is given, for example, to the type of DNA construct that would be required in order to drive expression of the nucleic acid in order to efficiently produce virus in an infected host such that a protective or therapeutic immune response is induced. Little guidance is provided as to how one could construct a nucleic acid encoding a productive HCV (i.e. a nucleic acid whose expression results in the production of virus by transfected cells) yet which is attenuated such that the pathologies associated with hepatitis infection are not produced. The specification merely indicates that attenuated viruses can be achieved by serial passage on appropriate cell lines. No guidance is given with regard to modification of specific regions of HCV that would result in such an attenuated virus.

The existence of working examples: The working examples are solely directed towards demonstrating that at least some full-length clones of HCV can be productive if introduced directly into the liver of chimpanzees. Not all of the exemplified full-length clones are infective in vivo. Indeed, even within the complex "quasi-species" of HCV clones obtained from infected animals, not all of the nucleic acids obtained from a single animal are infective. It is not at all clear from the working examples that one can necessarily predict which clones will produce virus upon transfection and which ones will not. No other means of introducing nucleic acids into the cells of an animal, other than by direct injection into the liver, are exemplified in the specification.

State of the art: At the time of filing for the instant application there appear to have been no known vaccines effective for the treatment of animals infected by HCV or effective in the prophylactic protection against HCV infection. At the time of filing for the instant application there appears to be little guidance with regard to the productive transfection of cells in vivo with nucleic acids encoding HCV such that an attenuated virus that does not cause pathology is produced. Indeed, at the time of filing the level of understanding the pathogenesis of hepatitis C was underdeveloped. The prior art teaches "Despite great progress in understanding the natural history of the disease, fundamental aspects of the pathogenesis of hepatitis C remain unknown." (Nelson Fausto, American Journal of Pathology, August 1997, Vol. 151, No. 2, page 361, first column). The only animal model system for studying HCV infection is the chimpanzee. It is unclear from the prior art how closely HCV infection in the chimpanzee follows the events of human HCV infection. Also, it is unclear how closely results seen for the generation of a protective or therapeutic immune response against HCV in chimpanzees in response to transfection with a nucleic acid composition will carry over to humans.

Predictability of the art: Given that an effective vaccine, much less a nucleic acid-based vaccine, has yet to be produced against HCV; given that the prior art and specification do not make clear what specific changes can be made to produce a nucleic acid whose expression will result in an attenuated virus; and given that it is not at all clear that results seen in the chimpanzee model system will necessarily carry over to humans, it would be unpredictable before hand as to whether a particular nucleic acid construct will function in vivo to produce an attenuated virus as well as producing a protective or therapeutic immune response.

The amount of experimentation necessary: Given the whole of the factors discussed above, it would've required undue, unpredictable experimentation for one of skill in the art to practice the claimed invention at the time of filing. If one of skill in the art wanted to practice the claimed method with humans, for example, one of skill in the art would have to first envision a particular nucleic acid sequence encoding an HCV virus, envision an appropriate construct to drive expression of the nucleic acid sequence in target tissue such that attenuated viruses are produced upon transfection and construct the particular nucleic acid sequence/construct. One would then have to test the construct for its ability to produce viruses upon transfection of target cells (e.g. in chimpanzees). If unsuccessful, which is likely given the lack of guidance provided by the specification and prior art as to which nucleic acids will cause production of viruses upon transfection into host cells and based upon applicants' own results that indicate that even within the "quasi-species" of clones isolated from a single animal not all clones are infective, one would then have to either envision a modification of the first construct/means of delivery/dose, etc., or envision an entirely new combination of nucleic acid construct/means of delivery/dose and test the modified or new combination of nucleic acid construct/means of delivery/dose to determine if virus is produced following transfection in vivo. If unsuccessful, which is likely given the lack of guidance provided by the specification and prior art as to which nucleic acids will cause production of viruses upon transfection into host cells and based upon applicants' own results that indicate that even within the "quasi-species" of clones isolated from a single animal not all clones are infective, the skilled artisan would have to repeat the entire unpredictable process until a combination of nucleic acid construct/delivery means/dose is identified.

Once a combination of nucleic acid construct/delivery means/dose is identified as producing virus upon transfection in vivo, it will be necessary to determine the pathological effects of virus production on the animal model (i.e. in chimpanzees). If the nucleic acid construct does not encode an attenuated virus with regard to the pathologies associated with HCV infection, which is likely given the lack of guidance in the prior art or specification as to how one would actually construct a nucleic acid encoding an attenuated HCV virus and given the underdeveloped state of the art with regard to the pathogenesis of hepatitis C, one of skill in the art would have to start over at the beginning by envisioning a modification of the first combination of nucleic acid construct/delivery means/dose, or a completely new combination of nucleic acid construct/delivery means/dose and repeat the entire unpredictable process to identify a second combination of nucleic acid construct/delivery means/dose resulting in virus production upon transfection in vivo. Once again, the skilled artisan would have to then determine the toxic effects of the virus on the host animal. If the nucleic acid construct does not encode an attenuated virus with regard to the pathologies associated with HCV infection, which is likely given the lack of guidance in the prior art or specification as to how one would actually construct a nucleic acid encoding an attenuated HCV virus and given the underdeveloped state of the art with regard to the pathogenesis of hepatitis C, one of skill in the art would have to start over at the beginning and repeat the entire unpredictable process until a nucleic acid construct/delivery means/dose combination is identified that results in the production of an attenuated virus.

If finally successful in identifying a combination of nucleic acid construct/delivery means/dose effective in producing an attenuated virus upon transfection of target cells in vivo, one of skill in the art would have to determine whether the combination results in a protective

immune response for animals not already exposed to the virus and in a therapeutic response for animals already infected with HCV. If unsuccessful in generating a protective or therapeutic immune response with the identified nucleic acid/delivery means/dose in the animal model, which is likely given that an effective vaccine against hepatitis C infection does not appear to have been disclosed in the prior art or instant specification, one of skill in the art would have to start at the beginning and repeat the entire, unpredictable process to identify a combination of nucleic acid construct/delivery means/dose that results in production of an attenuated virus and effective immune response upon transfection into the target cells of an animal.

Finally, if a combination of nucleic acid construct/delivery means/dose were identified in the model system (i.e. the chimpanzee), the combination would then have to be tested in humans. It is noted that it is likely that a new means of delivery of the nucleic acid construct to target tissues will have to be developed because the only exemplified example in the specification and prior art appears to be direct injection of the nucleic acid encoding HCV into the liver. It is unlikely that this means of delivery is going to be acceptable for use in humans. Even aside from the probable necessity of developing an entirely new combination of nucleic acid construct/delivery means/dose for humans, it is unclear whether the results found in the chimpanzee model system for induction of an immune response by transfection with a nucleic acid encoding an attenuated virus will necessarily be predictive of success in humans. Therefore, practicing the claimed methods in humans with a nucleic acid construct found to produce an effective immune response in chimpanzees without pathological effects is unpredictable.

Given the extraordinary amount of unpredictable experimentation necessary to practice the claimed invention, it would require undue, unpredictable experimentation to practice the

claimed methods of producing a therapeutic or protective immune response in animals by administration of a nucleic acid encoding an HCV. Therefore, the instant specification is not considered enabling for the rejected claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-45, 48, 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42, 48, 51 and 53 are vague and indefinite in that the metes and bounds of the phrase "a suitable amount of a pharmaceutically acceptable diluent or excipient" are unclear. The term "suitable amount" does not appear to be clearly defined in the specification with regard to diluents or excipients. It is likely that what an investigator considers a "suitable amount" for a particular excipient or diluent will differ from investigator to investigator. Since the words "suitable amount" do not appear to add anything to the phrase, it would be remedial to delete the words "suitable amount" from the claim language.

Claim 48 is vague and indefinite in that the metes and bounds of the phrase "wherein a fragment of said molecule which encodes the structural region of hepatitis C virus has been replaced by the structural region from the genome of another hepatitis virus strain" are unclear. The phrase is unclear in that it appears to specify that a nucleic acid sequence is replaced with a polypeptide sequence comprising the structural region of an HCV virus. It would be remedial to amend the claim language to clearly indicate that the nucleic acid fragment is replaced with

another nucleic acid fragment that encodes the corresponding structural region of a different hepatitis C virus.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
April 7, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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